Abstracts (01 July 98)

(presented in the same order as the program)

SESSION ONE: Uncertainty in Hazard Identification

1.1 The Scientific Basis and Methodologic Prerequisites of experimental studies for Detecting and Quantifying Carcinogenic Risks

Cesare Maltoni, Fiorella Belpoggi, European Ramazzini Foundation for Oncology and Environmental Sciences, Bologna, Italy

Experimental studies on laboratory animals (long-term carcinogenicity bioassays) represent a major tool for identifying and quantifying the exogenous (and more specifically industrial) carcinogenic agents/factors/situations. The level of precision of the results of carcinogenicity bioassays, as well as the degree of extrapolability of such results to human scenarios and pathologies, depend on a series of factors, which must all be equally considered with a view to producing adequate data, which in turn may constitute a solid scientific basis for carcinogenic risk assessment, regulations and prevention strategy.

The factors include: 1) the type of test animals, avoiding species and strains with excessive susceptibility to developing specific tumours (a situation which is remote from any human counterpart); 2) the use of more than one type of test animal, with complementary susceptibility to developing a variety of specific tumours; 3) the potency of the carcinogenic risk in question; 4) the size of the experimental groups, which is crucial in identifying and quantifying the risk from weak carcinogens or from exposure to very low doses of carcinogens of whatever potency; 5) the route of administration; 6) the range of the doses tested; 7) the duration of treatment; 8) the duration of the biophase; 9) the precision and standardization of experimental procedures, including monitoring the exposure and pathology examination.

In our opinion experimental carcinogenicity bioassays should be protracted for the whole life-span, and not truncated at an arbitrary time. For any comparison of the relative risk from exposure to different carcinogens, standardization of procedures within the same laboratory is a prerequisite. Many of the present uncertainties in risk assessment of carcinogenic risk depend on the inadequacy of the available experimental studies.

1.2 Epidemiolcgic Studies to Assess Diffuse Cancer Risks: The Case of ELF Radiation.

Anders Ahlbom, Karolinska Institute, Stockholm, Sweden

The first study suggesting that exposure to ELF magnetic fields might increase the risk of childhood leukemia was published about two decades ago. This study has been followed by more than a dozen studies that generally have confirmed the results of the original study. Despite this, most reviewers agree that causality is not proven. Three reasons for this are: 1) The magnitudes of the observed associations are modest; 2) It is unclear whether the types of exposure that give

the more consistent associations are the more accurate ones; and 3) There is no good candidate for a biological explanation as to how weak ELF magnetic fields would cause cancer; indeed, some even consider such an association implausible.

This gives risk to several questions: 1) Is there any type of finding from a further epidemiological study that would change the literature such that the conclusion that weak ELF magnetic fields are carcinogenic would be warranted and if so, how should such a study be designed? 2) What type of laboratory finding would be required for a similar change in the evaluation of the literature? 3) How is uncertainty in hazard identification handled with respect to risk assessment and risk communication as compared to how uncertainties in exposure measurement and dose-response modeling are handled?

1.3 Mega-Experiments to Identify and Assess Diffuse Carcinogenic Risks

Morando Soffriti, European Ramazzini Foundation for Oncology and Environmental Sciences, Bologna, Italy

The milestones of environmental and occupational carcinogenesis deal mainly, if not exclusively, with circumscribed populations exposed to high carcinogenic risks. It is a fact that most exogenous carcinogens have been identified by the self-emergence of a clear increase in the incidence of specific tumours among certain exposed populations. Situations of high carcinogenic risk still remain a crucial problem.

However more and more frequently we are facing carcinogenic risk scenarios of a different, and certainly no less important, nature: the exposure to low yet diffuse risks to which large groups of population or even the entire population are exposed.

Identifying and quantifying carcinogenic risks that are expected to be low and widespread, entails many delicate problems for the epidemiological and experimental researcher. In the case of epidemiological investigations, for example, there are interferences with misleading factors, the need for widely studied groups and the availability of proper controls.

For what concerns the experimental approach one may simply state that, at present, the format of the experiments ordinarily used is inadequate and even obsolete for the purpose of assessing the risks of low diffuse carcinogenic exposure.

The only possible approach, at least for major situations of low diffuse carcinogenic risk, is the use of mega-experiments, i.e. experiments based on large groups of animals, exposed throughout their lives and even transplacentally, protracted for the whole life-span so as to allow for the expression of all neoplastic potentialities, performed on animals whose spontaneous pathologies must be well known and defined. For many years such experiments have been going ahead at the Cancer Research Centre of the European Ramazzini Foundation, covering a variety of such risk scenarios. Some of them will be presented and commented.

1.4 Linking Science to Decisions: A Strategy for Electric and Magnetic Fields

Christopher Portier, National Institute of Environmental Health Sciences, North

Carolina, USA.

The degree to which an organization, agency or government evaluates risks from exposure to environmental agents is dependent upon a number of factors (e.g. extent of exposure, potential magnitude of risk, degree of public concern). Certain environmental agents require very careful review because their exposure is widespread, the potential economic impact of remediation is very high and there is great concern in the general population about the potential risks. One such agent is extremely low frequency electric and magnetic fields (ELF-EMF). The National Institute of Environmental Health Sciences (NIEHS) and the Department of Energy (DOE) are coordinating the implementation of the Electric and Magnetic Fields Research and Public Information Dissemination(RAPID) Program. RAPID was established by the 1992 Energy Policy Act (Section 2118 for Public Law 102-486) which was signed in October 1992. This five year effort is designed to determine if there are potential health effects from exposure to 60 Hz electric and magnetic fields (especially those produced by the generation, transmission and use of electric energy). The NIEHS is responsible for the development and implementation of a research program on the possible adverse human health effects of electric and magnetic fields and is required to report on the extent to which exposure to electric and magnetic fields adversely affects human health. In concert with a variety of public health agencies, industry groups and the public, the NIEHS has developed a process for the evaluation of the scientific literature associated with risks from exposure to ELF-EMF in homes due to power delivery and use. This process describes a series of open, public meetings and review criteria through which the NIEHS is seeking advice from the scientific community on the degree to which ELF-EMF poses a health hazard. This process combines a critical evaluation of the scientific literature with an assessment of the strength of the evidence for human health effects resulting from ELF-EMF exposures. This presentation outlines some of the practical problems associated with the evaluation of scientific evidence for a high-profile environmental health concern and discusses statistical and scientific issues which helped to reduce the uncertainty and lead to a clearer description of the strength of the evidence.

1.5 Long-Term Chemical Carcinogenesis Bioassays Predict Human Cancer Hazards: Issues, Controversies, and Uncertainties

James Huff, National Institute of Environmental Health Sciences, North Carolina, USA

Chemicals - both natural and synthetic - cause cancer. Because not all or even a majority of chemicals cause cancer, we must be able to identify with reasonable certainty those relative-ly and proportionately few that do. Carcinogenesis bioassays using laboratory animals have a solid history for identifying those agents as being most likely or predictive to be carcinogenic to humans: natural and synthetic chemicals, mixtures of chemicals, drugs, and commercial products [Huff, 1992; Fung et al.,1993, 1995; Huff et al., 1988, 991; Huff 1994a; IARC, 1998; Huff, 1998a,b]. Tellingly, nearly 30 agents causing cancer in humans were first found to induce cancer in animals [Huff, 1993a]. Unfortunately, however, bioassays have not been nor can they be used to evaluate or discover industrial processes or occupational exposure circumstances that cause or might cause cancer in humans [Tomatis et al., 1989; Huff, 1998b; IARC, 1998]. Equally difficult to test for carcinogenesis are environmental mixtures, dietary factors, foods, and actual human exposures to myriad and multiple chemicals, coupled with varied life styles and socio-economic situations [Huff, 1994b; Huff et al., 1996; Tomatis et al., 1997; Huff and Barrett, 1998]. Thus, we are obligated most often to test single or combination chemicals for possible carcinogenesis, increasing the importance of selecting the most appropriate and public health warranted chemicals to test.

Despite these obstacles, all chemicals known to cause cancer in humans that could be tested adequately in animals are likewise carcinogenic [Huff and Rall, 1992; Huff, 1994a]. Does this imply that any chemical that causes cancer in animals will be carcinogenic in humans? No. Carcinogens are not equal, and each must be evaluated regarding all relevant information and the strength of the carcinogenesis evidence. In fact, using a multi-factorial matrix approach including mechanistic information, exposures, and degrees and potency of responses, we have predicted only 5-10% of all chemicals would eventually be considered reasonably anticipated to cause cancer in humans [Fung et al., 1995]. The resultant number of carcinogens would be indeed large; yet, Importantly, most agents tested in animals do not cause cancer under conditions of long-term bioassays [Huff & Hoel, 1992; Huff, 1993b; Huff, 1998a,b,c; Huff and Soward, 1998]. Conversely, several experimental anti-carcinogens have been identified in routine bioassays [e.g., Douglas & Huff, 1984; Abdo et al., 1988; Chhabra et al 1994; Haseman and Johnson, 1996; Chan et al., 1996], that could be pursued for purposes of preventing cancer. Likewise, in foods there may be mutagens and carcinogens as well as antimutagens and anticarcinogens, especially in fruits and vegetables, that in composite tend to be preventative. Moreover, to test only one ingredient of a food [e.g., d-limonene in oranges] without testing all factors in that food can and often leads to incomplete or misleading conclusions. Thus, under most circumstances, composite foods should be tested for possible carcinogenic effects, rather than simply on select constituents.

Prudent public health policy obligates us to continue with the rationale strategy of reducing or eliminating exposures to chemical carcinogens, to chemicals in general, and to unhealthy workplace circum-stances [Tomatis et al, 1997]. Additionally, we need to persevere in our efforts to reduce or eliminate unnecessary industrial emissions [more than 2.2 billion pounds are released per year in the US] and chemical contaminations of our air; animal and plant life; lands and food crops; waters and fishes; and diets [Maltoni, 1997]. Consequently, cancer incidences and mortalities related to and influenced by chemicals, as well as other chemically associated diseases, will be restricted, reduced, or eradicated. This goal we must continue to approach.

After all, doesn't public health and human decency commit us to keep our individual and corporate wastes confined, or at least to use and dispose of these dangerous materials properly and safely without undue harm to others? More faithfully doing these recovery or recycling processes would reduce substantially the amounts of hazardous chemicals being released to our environments. And a subsequent reduction in exogenous cancer risk factors, leading to lessened morbidity and mortality from cancer.

Discussants: Eva Buiatti, Florence, Italy

SESSION TWO: Uncertainty in Exposure Assessment

2.1 Uncertainty in Kinetic Modelling and Biomonitoring

Lutz Edler, German Cancer Research Center, Heidelberg, Germany.

Physiologically-based pharmacokinetic models (PBPK models) are playing an

increasing role in quantitative risk assessement for tissue dosimetry, metabolic pathways and induction and modulation of regulating proteins. They are useful both for the prediction of biologically effective doses and for the modelling of the first steps of the toxic pathways of a substance identified to be hazardous to humans. Their interface character - located betwe en an exposure scenario and a pharmacodynamic model - will be exhibited and demonstrated with the dioxin example. Emphasis will be given to uncertainties observed for the exposure assessment in occupational cohorts exposed to dioxins and consequences for the usually much lower environmental exposure will be exhibited. A sample of previous exposed 192 workers in chemical industry will be be used for the exemplification.

Sources of uncertainty will be identified on the level of the model specification, of model parameter determination and the statistical and computational realization of the model fit and the model prediction. Methods for dealing with population heterogeneity in pharmacokinetic modelling will be addressed as well, e.g.through the Bayesian paradigm of statistical prediction.

2.2 Using Molecular Epidemiology to assess exposure

Paul Schulte, National Institute for Occupational Safety and Health, Ohio, USA

Molecular epidemiology involves the use of biological markers in epidemiology research and risk assessment. The molecular appellation is indicative not just of molecular, but also cellular and physiologic biomarkers. All of these types of biomarkers can be used in the various areas of risk assessment and risk characterization. Hence, there are examples of biomarkers being used to indicate exposure and supplement external exposure data; to serve as outcome variables in exposure-response relationships; or as sentinel early warning indicators of hazards. Biomarkers may also be used to reduce some of the uncertainty by corroborating external exposure data, assessing species comparability and explaining interindividual variability.

Although all these potential contributions of biomarkers are plausible, there are very few examples of risk assessment using biomarkers. If biomarkers are to be used to identify hazards, there is a need for them to be validated. In this regard they can be validated for exposure, effects indicative of disease, or susceptibility. Validation involves both a laboratory phase and a population phase. When biomarkers are validated, there still is a need for determining how to use them in risk assessment. This will involve questions about how to incorporate biomarkers data in models and how to analyze multiple molecular markers in the same or related pathways. Finally, there is the question of integration of biomarker and other data to predict quantitative risk. There is a need for further interdisciplinary approaches to address this question.

2.3 Kaplan Meier tumour probability as starting point for dose-response modelling provides accurate life-time risk estimates from rodent studies

Wil F. ten Berge, DSM, Heerlen, The Netherlands

The linearised multistage model for modelling the dose-response for specific tumour incidence has limitations in accuracy. This note provides an alternative basic method for analysing the dose-response relationship for specific cancers in long-term rodent studies. It is based on an actuarial analysis of mortality and specific tumour incidence. The survival and the Kaplan-Meier specific tumour probability are fitted to a Weibull model, in which exposure level, exposure period and observation period are independent variables. The mortality from specific cancers at a certain point in time is simulated by means of the product

of survival and specific tumour rate (derivative of Kaplan-Meier tumour probability) as function of exposure level, exposure duration and observation period, integrated over the observation period.

The model is demonstrated by means of fitting the mortality and tumour incidence data of the second NTP mice study on butadiene to a Weibull model and to the linear so-called one hit model. It will be shown, that in the experimental exposure range the Weibull model is far superior to the one-hit model and predicts the specific tumour incidence with a high accuracy over the total dose range.

The model of the Kaplan-Meier probability for a specific tumour is also useful for regulatory risk estimation. It is proposed, that a risk level for developing a specific tumour of 1 on 1000 over life time is about equal to 5 on 10000 at 50% survival of the population. The Kaplan-Meier probability may be estimated at the time of 50% survival of the exposed population, which is to be deduced from the all mortality data. This way of estimation provides meaningful data, using exposure level, exposure duration and observation period properly.

The advantage of the method of actuarial analysis for interpretation of rodent studies is, that allowance is made for competition between death causes, which is essential in case of considerable difference in mortality and specific mortality between dose groups. Integrating the product of survival and specific tumour rate is the proper way to predict in a comparative way mortality and specific mortality in an exposed and non-exposed rodent population.

2.4 Uncertainty in estimation of exposure using a toxicokinetic model. The example of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

Alberto Salvan, National Research Council, Padova, Italy.

The use of toxicokinetic models makes it possible to construct exposure parameters that may be more closely related to the individual dose than traditional measures of exposures to toxic agents. However, the process introduces a wide array of sources of uncertainty. Selecting a model structure to describe the kinetics of a toxic agent implies necessarily the use of simplifications and assumptions that will influence the range of applicability of the model. Once a model has been selected, the value of certain model parameters (constants) will be assigned, e.g. from anthropometric data, and the question arises of how sensitive the model predictions are to variations in the value of these constants. Next, other model parameters, typically those describing the kinetics of the agent, may be estimated from actual data. There may be limitations in the data, regarding for example sparseness (i.e. few observations per subject) and missing values. The methods used for parameter estimations will carry their own set of assumptions which need to be appropriate to the situation at hand. The dioxin example will be used to characterize the sources of uncertainty at each of the steps outlined above. The example will be based on a minimal toxicokinetic model used to estimate individual profiles of serum TCDD over time in a cohort with occupational exposure to dioxin.

2.5 The relative impacts of uncertainty in exposure assessment and analytical methods in dose-response modelling, with illustrations from a study of occupational exposure to magnetic fields.

Hans Kromhout, Wageningen Agricultural University, Wageningen, The Netherlands /Dana Loomis, University of North Carolina, North Carolina, USA

The relative importance of uncertainties in exposure assessment and the analytical treatment of exposure data in dose-response modelling is largely unknown. Sensitivity analyses provide the means for disentangling these two crucial stages in every occupational epidemiological study.

Choosing the wrong exposure measure will often lead to attenuation of or imprecision in the dose-response relation. Examples from a few studies on dust will be used to illustrate this very common problem, that often will occur whenever a complex exposure situation is present or the etiologic pathway unknown.

Large temporal variability is intrinsic to occupational and environmental exposures and must be handled appropriately. Although large variability in exposure concentrations can lead to measurement error, with its attendant bias and imprecision, it can also enable the researcher to optimise the exposure assessment. Understanding the components of variability in exposure concentrations and knowledge of factors affecting exposure levels will be crucial in this process. Exposure assignment to study subjects based on information like job history is presumably rather straight forward. However, the effect of using different lag periods, time windows and the like will not always be easily understood.

In a study on brain cancer among utility workers we tried to optimise both the way (historical) exposure to magnetic fields was estimated and the way the assigned exposures were consequently used to estimate dose-response relations. In order to estimate the relative impacts of both essential steps in the epidemiological study we applied sensitivity analyses. The results showed that the way the exposure data was treated prior to assignment to individual workers had far more impact on the estimated dose-relationship than subsequent treatment of the exposure measures in the dose-response analyses. So far, it is unclear whether this observation will appear to be common. However, exposure assessment procedures and analytical strategies should be looked at carefully since they may explain a lot of the differences seen in the outcome of studies studying the same health effects of similar occupational and environmental exposures.

2.6 Measures of exposure to environmental tobacco smoke - validity, precision and relevance

Alistair Woodward, Wellington School of Medicine, New Zealand

It is often not clear what are the best measures of exposure for a risk assessment, or even how one should decide how to answer the question. Environmental tobacco smoke (ETS) provides a good example. Atmospheric monitoring of ETS suffers from a number of shortcomings. Monitoring equipment has been, in the past, relatively cumbersome and intrusive. There is no global measure of ETS - exposure to different components will vary widely in the same setting according to the factors influencing dispersion and decay of smoke. However the major difficulty lies in extrapolating from the quantity of smoke absorbed by a machine (generally stationary, and operated over a short time period) to the quantity inhaled in the longterm by a mobile individual. The considerable variation between individuals in distribution and metabolism of nicotine clouds the relation between the dose of ETS and biochemical measures in blood and other body

fluids. Furthermore, the relatively short half-life of nicotine in the body means that levels from spot samples do not provide a reliable guide to longterm exposure, and biochemical measures of exposure have little relevance to policy concerns.

Questionnaires obviously provide an imperfect measure of exposure to ETS. However they provide the only means of studying the large populations which may be required to identify health risks. Moreover, there is no gold standard by which to measure exposure to ETS: biochemical markers are precise and "objective", but describe only one facet of smoke exposure, and it is not yet known which constituents of ETS are most important in the aetiology of disease. It may be that the less precise but more wide-ranging measure of exposure provided by questionnaire is a better predictor of health effects than are the available biochemical markers, singly or in combination.

2.7 The contribution of environmental monitoring in the epidemiological assesment of exogenous risk: the experience of the A.R.P.A. of the Emilia-Romagna Region

A. Zavatti, Italy

Discussant: Paul Schulte, National Institute for Occupational Safety and Health, Ohio, USA

SESSION THREE: Uncertainty in Dose-response Modeling

3.1 Combining Uncertainty Factors in Setting Allowable Exposure Levels

Ralph Kodell, National Center for Toxicolgical Research Arkansas, USA

Acceptable levels of exposure to potentially toxic substances in environmental and occupational settings generally are based on data from animal experiments. Animal data are used to determine no-observed-adverse-effect levels (NOAELs) which are presumed to pose negligible or zero risk to animals, or benchmark doses (BDs) which are predicted to correspond to specific low levels of risk. Such NOAELs or BDs are reduced by a product of uncertainty factors to arrive at acceptable exposure levels for humans. The resulting exposure levels, often called reference doses (RfDs), are daily human exposure levels that are assumed to pose negligible risk of deleterious health effects. The most common uncertainty factors are: UA, a factor to account for uncertainty regarding the relative sensitivities of animals and humans; UH, a factor to account for uncertainty with respect to differential sensitivities among humans; US, a factor to capture uncertainty in extrapolating from subchronic-exposure data to the chronic-exposure situation; and UL, a factor to account for uncertainty in extrapolating from a low-risk level to a zero-risk or negligible-risk level, if a lowest-observed-adverse-effect level (LOAEL) is used in place of a NOAEL, or if a relatively high BD is used. Commonly, the default value for each source of uncertainty is 10, which is the maximum value considered in practice. Recent work

by various authors has shown that these uncertainty factors behave as random variables with approximate lognormal distributions. Estimated means and standard deviations of the distributions of log-uncertainty factors provide sufficient information to enable the calculation of statistical confidence limits for the product, UA(UH(US(UL. This enables one to choose a combined uncertainty factor that assures adequate coverage of the uncertainty distribution, and to assess the coverage provided by the conventional approach of using a product of default factors.

3.2 Statistical methods for developmental toxicology

Louise Ryan, Harvard University, Massachusetts, USA

This talk will begin with an overview of the kinds of statistical issues that arise in the analysis of data from developmental toxicology studies. We will then discuss some recent developments related to the analysis of multiple outcome data as they arise in this setting. Methods will be illustrated with data from several real studies, including one recently completed on reproductive effects of inhaled ethylene oxide. Several areas of needed future research will be outlined.

3.3 Sources of uncertainty in dose-response modeling of epidemiologic data for risk assessment

Leslie Stayner, National Institute for Occupational Safety and Health, Ohio, USA

Epidemiologic data is increasingly being use for dose-response analysis for risk asssessment purposes. The EPA and other U.S. and International agencies have clearly expressed a preference for using epidemiologic data rather than toxicologic data when possible. However, there are a number of important sources of uncertatiny in using epidemiologic data for this purpose that need to be clearly recognized. This paper presents a critical review of these sources of uncertainty and uses several examples from occupational studies to illustrate these issues.

The primary sources of uncertainty in using epidemiologic data results for dose-response analyses are related to the design of the studies, which are by necessity non-randomized. This failure to be able to randomize exposures results in potential for confounding, selection bias and other forms of biases. Limitations in epidemiologic studies due factors such as inadequate or incomplete followup (i.e. latency), and inadequate sample size may further limit the usefullnes and introduce subtantial uncertainty into the risk analysis.

The correct specification of the exposure-response model is another major souce of uncertainty in epidemiologic exposure-response models. Numerous parametric, non-parametric and biologic models may be used to model the relationship between exposures and disease. However, how does one decide what is the best model? Criteria of goodness of fit or biologic criteria may be used, but one is often left with a number of plausible models. Examples from modeling asbestos and cadmium exposure will be used to illustrate the large range of uncertainty related to model selection.

The choice of the appropriate epidemiologic study may introduce additional

uncertainties when there are multiple epidemiologic studies with exposure-response information. Meta-analysis or pooling methods may be used to summarize the exposure-response information in the multiple studies. However, there is frequently substantial heterogeneity in the slopes from these studies and it may frequently difficult to produce one slope estimate. A meta-exposure-response analysis of luekemia, brain cancer and electromagnetic frequency (EMF) exposure will be used to illustrate this.

Last, but certaintly not least, errors in exposure estimates in epidemiologic studies may frequently introduce substantial uncertainty into exposure-response analyses. Historical data on exposures are frequently absent or of limited quality. An analysis of diesel exhaust and lung cancer will be used to illustate Monte Carlo methods that may be used to assess the extent of uncertainty in occupational historical cohort mortality studies.

3.4 Nonparametric analysis of a dose-response relationship

Kurt Ulm, Institut fuer Medizinische Statistik und Epidemiologie, Munich, Germany

The analysis of a dose-response relationship is an important criterion on the way to establish causality. Additionally it is also necessary for the quantitative risk assessment. There are many different models available which can be used to estimate the relationship. But there are situations where the results from the various models are different. A special problem occurs when a threshold value has to be estimated. In order to solve this problem a nonparametric method, the isotonic regression can be applied. This method together with some applications will be presented. The result of the isotonic regression is compared with that of other models. The analysis will include data on para-aramid, dust and silica.

3.5 Characterization of Uncertainty and Variability in Residential Radon Cancer Risks

Daniel Krewski, S. Rai, J. Zielinski, Health and Welfare Canada, Ottawa, Canada

Radon, a naturally occurring gas found at some level in most homes, is an established risk factor for human lung cancer. The U.S. National Research Council (1998) has recently completed a comprehensive evaluation of the health risks of residential exposure to radon, and developed models for projecting radon lung cancer risk in the general population. This analysis suggests that radon may play a role in the etiology of 10-15% of all lung cancer cases in the United States, although these estimates are subject to considerable uncertainty. In this article, we present a detailed analysis of uncertainty and variability in estimates of lung cancer risk due to residential exposure to radon in the United States using a general framework for the analysis of uncertainty and variability that we have developed previously. Specifically, we focus on estimates of the population attributable risk (PAR), which reflects the proportion of the lung cancer burden attributable to radon, and on estimates of the age-specific excess relative risk (ERR), which varies substantially among individuals. Uncertainty in the PAR is determined predominantly by uncertainty about the values of the parameters in the risk models used to estimate the PAR; uncertainty in radon levels in homes and the dosimetric K-factors used to extrapolate from occupational to environmental settings contribute relatively little to uncertainty in the PAR. Variability in ERR is largely determined by variability in residential exposure patterns. These results suggest that reduction in uncertainty about the PAR for radon induced lung cancer can only be achieved if more reliable risk projection models can be developed.

3.6 Estimates of the Proportions of Carcinogens and Anti-Carcinogens in Bioassays Conducted by the U.S. National Toxicology Program (NTP)

Kenny Crump, ICF-Kaiser, Ruston, Louisiana, USA and Daniel Krewski, Health and Welfare Canada, Ottawa, Canada

A meta-analysis was performed to estimate the proportion of liver carcinogens, the proportion of chemicals carcinogenic at any site, and the corresponding proportion of anti-carcinogens among chemicals tested in approximately 400 long-term cancer bioassays conducted by the U.S. National Toxicology Program. The estimation procedure did not involve determination of the carcinogenicity of individual chemicals (and consequently did not focus on a particular false positive rate such as 0.05). The specific estimator used was [bF(a) - aF(b)]/(b-a), where F(p) was the empirical distribution function of p-values from one-tailed tests for positive trend derived from individual studies. This

estimator is negatively biased for all choices of a and b. Despite this bias, the study provided persuasive evidence for a larger proportion of liver carcinogens (0.43, 90% CI: 0.35, 0.51) than was identified by the NTP (0.28). Evidence for a larger proportion of chemicals carcinogenic at any site (0.59, 90% CI: 0.49, 0.69) than was identified by the NTP (0.52) was more limited. These differences appear to relate to the manner in which the NTP evaluates studies, and suggest that some uncertainty exists in the identification of a chemical as a carcinogen.

A larger proportion of anti-carcinogens (0.66) was estimated than carcinogens (0.59). Despite the negative bias, it was estimated that 85% of the chemicals were either carcinogenic or anti-carcinogenic at some site in some sex-species group. This suggests that most chemicals tested at high enough doses will cause some sort of perturbation in tumor rates.

Discussant: Christopher Portier, National Institute of Environmental Health Sciences, North Carolina, USA

SESSION FOUR: Uncertainty in risk characterization and communication,

4.1 Larger Lessons about Uncertainty

John Bailar, University of Chicago

Uncertainty in the detection and evaluation of chemical hazards to health is great and difficult to deal with. Some of the uncertainty has to do with data, some with incomplete understanding of processes, and some with the most fundamental ways of viewing the questions. True variability -- across space, in time, or among individuals -- complicates the search for understanding of many important aspects of risk. A few statistical and toxicologic tools are available to assess uncertainty, and three methods of classifying uncertainty will be

briefly discussed.

We rarely know as much as we think we do (and not just in risk assessment). Great uncertainty is likely to remain an important part of risk assessment for some decades to come.

4.2 Distributions of Individual Susceptibility among Humans for Toxic Effects -- For what Fraction of Which Kinds of Chemicals and Effects does the Traditional 10-fold Factor Provide How Much Protection?

Dale Hattis, Clark University, Massachusetts, USA

A significant data base has been assembled on human variability in parameters representing a series of steps in the pathway from external exposure to the production of biological responses:

- Contact Rate(Breathing rates/body weight; fish consumption/body weight)
- Uptake or Absorption (mg/kg)/Intake or Contact Rate
- General Systemic Availability Net of First Pass Elimination and Dilution via
- Distribution Volume
- Systemic Elimination/Clearance or Half Life
- Active Site Availability/General Systemic Availability
- Physiological Parameter Change/Active Site Availability
- Functional Reserve Capacity--Change in Baseline Physiological Parameter Needed to Pass a Criterion of Abnormal Function

This paper will discuss the current results of analyzing these data to arrive at estimates of overall distributions of human susceptibility for different types of chemicals (e.g. relatively lipophilic vs relatively hydrophilic), and different types of adverse effects (e.g., simple irritant responses, vs systemic toxicity, vs hypersensitivity reactions). The degree of protection will be very tentatively evaluated by projecting the incidences of effect that would be expected for a 10 fold lowering of dose from a 1-10% incidence level if the population distribution of susceptibility for the different chemical and effect types were truly lognormal out to the extreme tails.

4.3 Issues in Defining Confidence Intervals in Epidemiologic Studies on Carcinogenic Exposures

P. Comba, R. Pirastu, Istituto Superiore di Sanita, Italy; A. Salvan, O. Axelson

Epidemiologic studies occasionally report 90% confidence intervals for risk estimates, as opposed to the more conventional 95% intervals. A rationale for this "unconventional" choice, when given, is based on limited study-design features, such as one-sided vs. two-sided hypothesis testing. In this view, the choice between 90% and 95% confidence levels for risk estimation implies balancing the possible consequences of type I and type II errors. However, no consideration is usually given to other important study design features and how they are implemented. Although random error and study size are relevant to the interpretation of study results, study design and issues of confounding, selection bias, and measurement error need to be addressed as well. Notwithstanding the large body of literature addressing problems with the

statistical analyses of observational studies, the practice of reporting study results based on statistical testing (including the use of confidence intervals as tests) is still widespread. Conventional levels attached to probability statements regarding the association between disease and exposure are also increasingly used in judgments for compensation claims. The example of cancer associations involving exposure to asbestos is discussed.

4.4 Analysis of PBPK Models for Risk Characterization

Frederic Bois, INSERM, Paris

It is theoretically possible to disentangle uncertainty from variability in risk assessment, through appropriate statistical modeling (e.g. hierarchical modeling). Adoption of a Bayesian framework also permits the seamless integration of different kinds of information available to choose and parameterize risk models. Appropriate numerical techniques can be found, for example, in the arsenal of Markov chain Monte Carlo (MCMC) simulations. The recent developments in this area can actually be viewed as extensions of the "traditional" or standard Monte Carlo (MC) methods for uncertainty analysis. Arguments of sensitivity analysis, similar to those that apply to MC methods, favor the updating of all model parameters (i.e. the estimation of the joint posterior density of all parameters). The first part of this paper is devoted to a justification of the above claims. Examples of results are presented. The second part discusses several open problems related to: - Integration of exposure, internal dose, and effect models: Can they be considered separately? If yes, how do we deal with uncertainty and variability at their interface?

- Model uncertainty: How do we take it into account? - Interspecies and interpopulation extrapolations: What is the status of interspecies extrapolation in the proposed framework? Can we extrapolate uncertainty and variability separately? What is "interpopulation" extrapolation? How can we deal with it?

- Parameter identifiability: What happens in a population model when parameters are not identifiable for all subjects? - Covariance modeling: What are the different approaches to covariance modeling? Why do they matter?

4.5 Uncertainty in risk characterization of weak carcinogens

Nachito Yamaguchi, National Cancer Center Research Institute, Tokyo, Japan

The topic I have in my mind is the uncertainty in risk characterization of weak carcinogens. As is shown by the recent decision by the International Agency for Research on Cancer on the carcinogenicity of dioxins, questions are raised on the role of epidemiology in the risk assessment of weak carcinogens. In the overall evaluation of 2,3,7,8-tetrachloro-dibenzo-para-dioxin, IARC classified it as human carcinogen, though epidemiological studies provided only "limited evidence". Since the uncertainty in epidemiologic inference on carcinogenesis lies on the multi-factorial and multi-step nature of disease process as well as the uncertainty in measurement and statistical errors, there seem to be two different approaches to overcome the uncertainty inherently existing in epidemiological inference. First, the uncertainty should be reduced by more reliable study design with accurate measurements of exposure and outcome. The recent development in molecular epidemiology might be able to play a substantial role in this context. The other possible approach is the modeling of disease process based on available knowledge. In the case of dioxins, the probable mechanism of action is believed to be through the binding of dioxins to Ah receptor, but the modeling of these mechanistic features is yet to be developed.

In my presentation, I would like to challenge the uncertainty of risk assessment from epidemiological viewpoints. In particular, I would like to discuss the role of modeling approaches to reduce the uncertainty in epidemiological inference. I believe the modeling approach would be powerful to integrate the knowledge obtained by basic research into epidemiologic inference. This has been proved so, for example, in the field of toxicology and pharmacology. The attempt I will make is to critically review the possibility of this approach in the risk assessment of carcinogens, with special reference to the problem of dioxins.

4.6 Reducing Uncertainty in the Derivation and Application>of Health Guidance values: dioxin as a case study

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In response to a request from the U.S. EPA to clarify the relationship ATSDR's MRL, Action Level, and EMEG for dioxin, we developed a document entitled *Dioxin and Dioxin-Like Compounds in Soil, Part I: ATSDR Interim Policy Guideline* as well as a supporting document *Dioxin and Dioxin-Like Compounds in Soil, Part II: Technical Support Document*. In these documents, we evaluated the key assumptions underlying ATSDR's development and use of its Action Level, MRL, and EMEG for dioxin, described the chronology of events outlining ATSDR's development and use of these different health guidance values for dioxing, and identified the areas of uncertainty surrounding these values. Four scientific assumptions were found to have a great impact on this process; these were: (1) the specific uncertainty factors used, (2) the TEQ approach, (3) the fractional exposure from different pathways, and (4) the use of body burdens in the absence of exposure data. This information was subsequently used to develop a framework for reducing the uncertainties in public health risk assessment associated with exposure to other chemical contaminants in the environment. Within this framework are a number of future directions for reducing uncertainty, including physiologically-based pharmacokinetic modelling (PBPK), benchmark dose modelling (BMD), functional toxicology, and the assessment of chemical mixture interactions.

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Summarization, and Closing

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